Critical Care

COMMENT

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Do prolonged infusions of β-lactam antibiotics improve outcomes in critically ill patients with sepsis? It is time to say yes

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Sepsis remains an important global health problem and a leading cause of death in critically ill patients worldwide [1]. The β-lactam antibiotics are widely used as an important component of antibiotic therapy for patients with sepsis. The bactericidal activity of β-lactam antibiotics is typically time-dependent, and their clinical effectiveness is affected by the duration of the free drug concentration remains above the minimum inhibitory concentration (MIC) of the target pathogen. Therefore, the prolonged (Extended or continuous) infusion of β-lactam antibiotics has been an attractive strategy, because it provides a more stable free drug concentration and a longer duration of free drug concentration above the MIC [2]. Many previous studies have shown pharmacological rationale and potential clinical advantages in favor of prolonged infusion of β-lactam antibiotics in critically ill patients with sepsis [3]. Therefore, many recent international consensus and guidelines recommend the use of prolonged infusion strategies for β-lactam antibiotics in critically ill patients [4–6]. And based on "moderate-quality" evidence, the Surviving Sepsis Campaign guidelines suggest a "weak" recommendation for prolonged infusion of β-lactam antibiotics for patients with sepsis or septic shock, rather than conventional intermittent infusion [7].

However, two well-conducted studies on this topic published in JAMA showed negative results. In the MERCY trial, a total of 607 patients were enrolled, and unfortunately there was no significant difference in the primary composite outcome or any secondary outcome between the two groups [8]. It may have been underpowered to detect small but still clinically meaningful results. Recently, the BLING III randomized clinical trial (RCT), the largest RCT on this topic to date, has been published [9]. Although only clinical cure was positive result in the continuous vs intermittent infusion group (55.7% vs 50.0%, respectively; $P<0.001$), the absolute 90-days mortality (24.9% vs 26.8%, respectively), hospital mortality (23.3% vs 25.0%, respectively) and ICU mortality (17.1% vs 18.4%, respectively) were lower in the continuous infusion group than that in the intermittent infusion group. Thus, adding those data from the BLING III trial to previous meta-analysis would support rather than refute the previously reported benefits.

Abdul-Aziz and colleagues performed a systematic review and meta-analysis on this topic, including 18 RCTs with 9108 critically ill adults with sepsis or septic shock. And the results showed that prolonged infusion of β-lactam antibiotics was associated with lower 90-days mortality, ICU mortality and an increase in clinical cure [10]. To further verify the reliability of the conclusions and avoid false positive or false negative results, we conducted trial sequential analysis (TSA) based on the work of Abdul-Aziz et al. We used a random effects model to construct the cumulative Z curve. TSA was performed to maintain an overall 5% risk of a type I error. According to previous high-quality RCTs on this topic, the 90-day mortality rate was set as 27.9% in the intermittent group and 24.7% in

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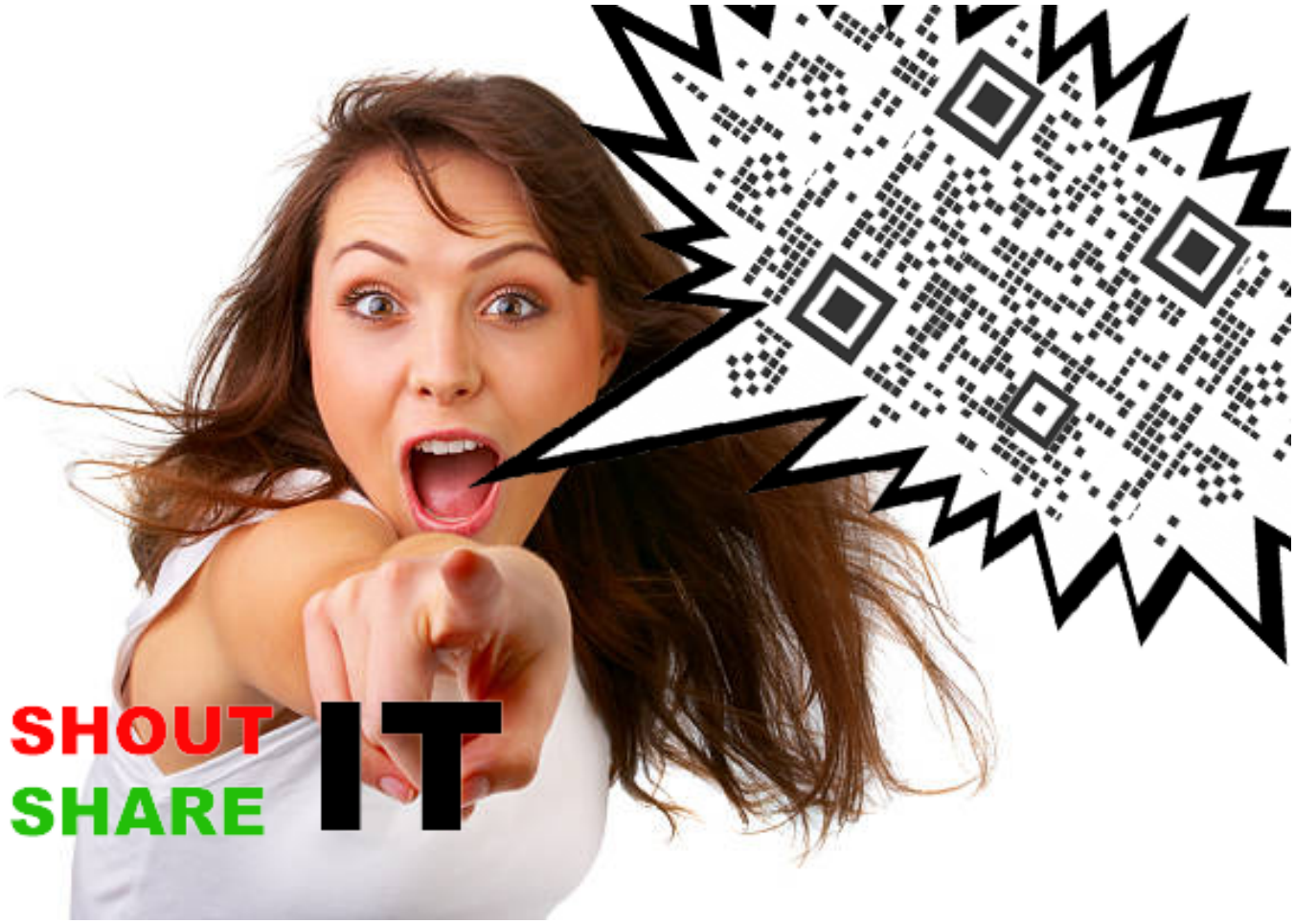
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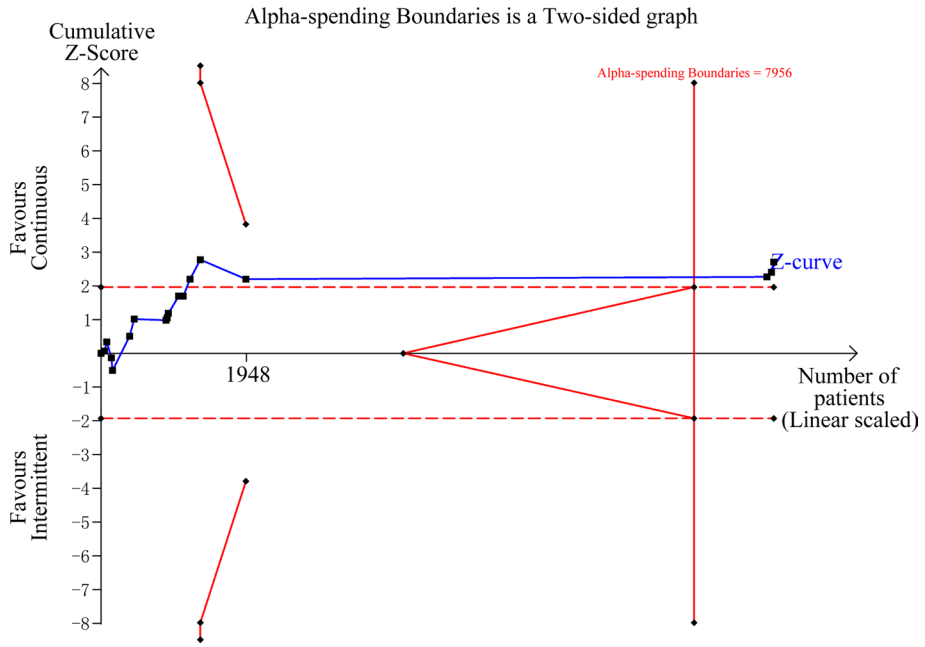

Fig. 1 Trial sequential analysis. The cumulative Z-curve (complete blue line) was constructed using a random effect model. The etched red line shows the conventional test boundary. The complete red line represents the trial sequential monitoring boundary. A diversity-adjusted information size of 7956 patients were calculated based on using alfa = 0.05 (two sided), beta = 0.10 (power 90%), an intervention event rate of 24.7%, and a control event rate of 27.9%. The cumulative Z-curve crossed the conventional test boundary and reached the required information size

the continuous group [8, 9, 11].And TSA result showed that the required information size was 7956. The cumulative Z-curve crossed conventional test boundary and reached the required information, indicating that the results of Abdul-Aziz et al. study are conclusive and require no further study (Fig. 1). Therefore, it is time to say yes that prolonged infusions of β-Lactam antibiotics can improve outcomes in critically ill patients with sepsis.

Abbreviations

MIC	Minimum inhibitory concentration
RCT	Randomized clinical trial
TSA	Trial sequential analysis

Author contributions

Xiaoming Li conceived the study, performed statistical analyses, and drafted the manuscript. Zhengying Jiang revised the manuscript.

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None.

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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